



**Bioforce Monograph**  
**AtroMed/Rheuma-Gel**

# Arnica

Arnika montana L.

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# Arnica

## 1.1 Botany

*Arnica montana* is a member of the sunflower family (Asteraceae). It is native to central and southern Europe<sup>1</sup> and occurs mainly in southern Germany, northern Italy and the Balkan states. *Arnica montana* grows to a height of about 50 cm, and has a tough course stem with a leaf rosette growing from close to ground level. Its yellow flower heads are surrounded by two layers of calyx covered in short shaggy hairs. The part used as herbal remedy is the entire, fully opened, fresh or dried flower head, which contains the pharmacologically active substances.<sup>2</sup> The plants prefer sandy, humus, peaty and low-lime alps up to 2800 m.<sup>3</sup>

## 1.2 Cultivation

Large areas of wildy occurring *Arnica montana* have become rare because of intensive collection and overfertilisation. For this reason, arnica has been included in the list of endangered plant species, and was placed under special protection by the Species Protection Agreement of Washington 1981. In many countries, the collection of the flowers is therefore forbidden.

Most of the currently available arnica herbal material is now obtained by cultivation, mostly of American field arnica, *Arnica chamissonis*, which is simpler to cultivate. However, *Arnica chamissonis* contains far fewer efficacy-determining ingredients than does *Arnica montana*.

Bioforce arnica extract comes from fresh flower heads of biologically certified cultivation, something which is essential for a uniform active substance content. After numerous unsuccessful attempts to cultivate arnica, Bioforce AG in cooperation with specialists finally managed this a few years ago in Germany. Success depended mainly on good soil ventilation, a good water supply, and a low content of free lime.

Concentrated field cultivation of *Arnica montana* has so far proven to be a considerable undertaking, as the high requirements of the plant make them sensitive to altered external influences. These problems are reflected in poor and irregular fertilisation, frequent plant failure, poor plant development, and susceptibility to disease.<sup>4</sup>

## 1.3 Traditional use

Contrary to expectations, the physicians of antiquity had no knowledge of arnica, and it cannot be guaranteed that the early mentions in mediaeval manuscripts actually refer to arnica.<sup>5</sup> The first definitely confirmed mention of arnica is in the Encyclopaedia of Matthaeus

Sylvaticus from the 14<sup>th</sup> century.<sup>6</sup> It is only from the 16<sup>th</sup> century that arnica was used externally as a «wound herb» in sprains, bruises, painful swellings, injuries and wounds.<sup>7</sup> At the start of the 19<sup>th</sup> century, arnica finally became a basic tool in the medical arsenal and started being commonly used. Toxic side effects with internal use reduced the wide-spread consumption, but arnica nevertheless remains an important phytotherapeutic.<sup>8</sup>

## 1.4 Current use

Today, *Arnica montana* is used exclusively in topical form for the results of accidents and injuries, such as haematomas, distortions, strains, bruises and fracture oedema.<sup>9</sup> Other uses include adjuvant treatment of chronic complaints such as rheumatism, arthritis, osteoarthritis and gout, as well as other joint and muscle inflammations and back pain.<sup>10</sup>

## 1.5 Pharmacology

Like other phytopharmaceutics, *Arnica montana* is also a mixture of different groups of substances that contribute to the overall action. It is undisputed that sesquiterpene lactones of the pseudoguaianolide type are the constituents with the strongest action<sup>11</sup> (Figure 1). This group includes helenalin and 11 $\alpha$ ,13-dihydrohelenalin, which are esterified with short-chain fatty acids. The origin of arnica species can be determined on the basis of their sesquiterpene lactone composition. Species from central Europe contain mainly helenalin, whereas dihydrohelenalin dominates in Spanish species.<sup>1</sup> Other accompanying substances include essential oils with free fatty acids and thymol derivatives, as well as phenolic compounds such as flavonoids and caffeoyl quinic acid compounds.

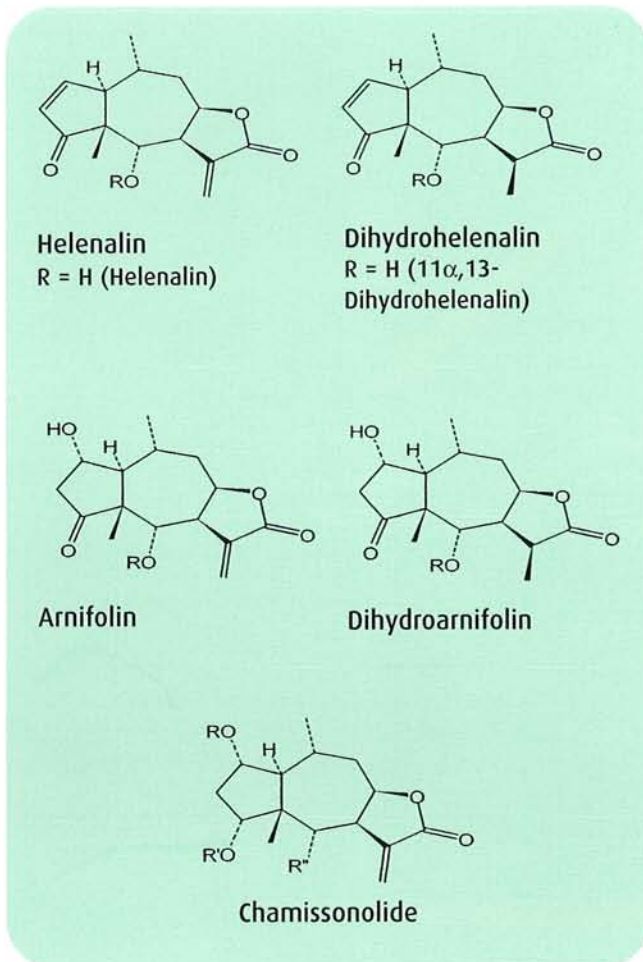


Figure 1: Sesquiterpene lactones in the flowers of *Arnica montana*

### 1.5.1 Anti-inflammatory action

The sesquiterpene lactones exert a strong anti-inflammatory action by intervening very early on in the inflammatory process.<sup>12</sup> Micromolar concentrations of helenalin, dihydrohelenalin and its ester derivatives inhibit the activation of transcription factors NF- $\kappa$ B (nuclear factor  $\kappa$ B) and NF-AT (nuclear factor of activated T cells).<sup>13,14,15</sup>

Transcription factor NF- $\kappa$ B causes expression of over 150 genes as a reaction to inflammatory, bacterial and viral processes. The activators of NF- $\kappa$ B and the type of expressed genes make it a key factor in the immune response in the human body.<sup>12</sup> NF- $\kappa$ B comprises the subunits p50 and p65, and is present in inactive form in the cytoplasm. The third subunit I $\kappa$ B prevents passage into the cell nucleus. In the event of inflammation or a bacterial or viral infection, the inhibitory subunit I $\kappa$ B is broken down, and NF- $\kappa$ B then passes into the nucleus, binds to the DNA, and initiates the formation of a variety of inflammation mediators (acute-phase proteins, proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-8 and tumour-necrosis-factor  $\alpha$  (TNF- $\alpha$ )).<sup>11</sup>

Helenalin also exerts an inhibitory action in this procedure by preventing NF- $\kappa$ B from binding to DNA. This occurs by Michael addition of helenalin to the subunit p65 of the transcription factors (Figure 2).<sup>16</sup>

Of the synthetic substances that are used to inhibit inflammation, only the highly potent glucocorticosteroids inhibit NF- $\kappa$ B. Other NSAIDs inhibit mainly the cyclo-oxygenases.

The inhibition of NF-AT by arnica preparations prevents the production of cytokines of the types IL-2, IL-3, GM-CSF, IFN- $\gamma$  and TNF- $\alpha$ . These mediators are also involved in the development of the inflammatory reaction.

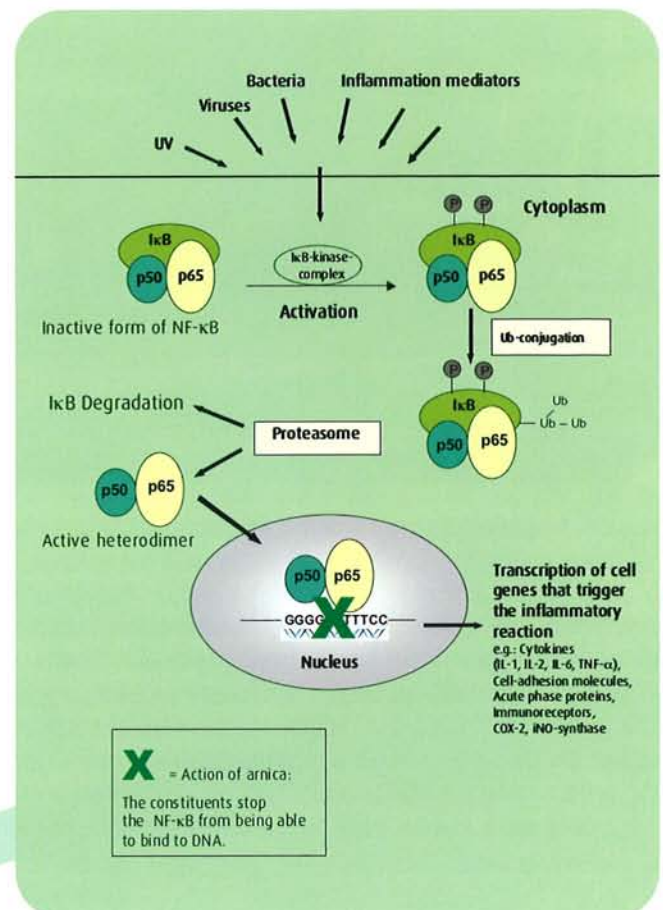


Figure 2: The NF- $\kappa$ B cascade and the site of action of arnica

In comparison with other anti-inflammatory substances, the sesquiterpene lactones inhibit the inflammatory process at what is essentially its point of origin. Non-steroidal anti-inflammatory drugs (NSAIDs) or base antirheumatic agents act only further along the inflammatory cascade at the level of the enzymes of the arachidonic acid metabolism. By this time, the inflammatory reaction is already fully started.<sup>16</sup>

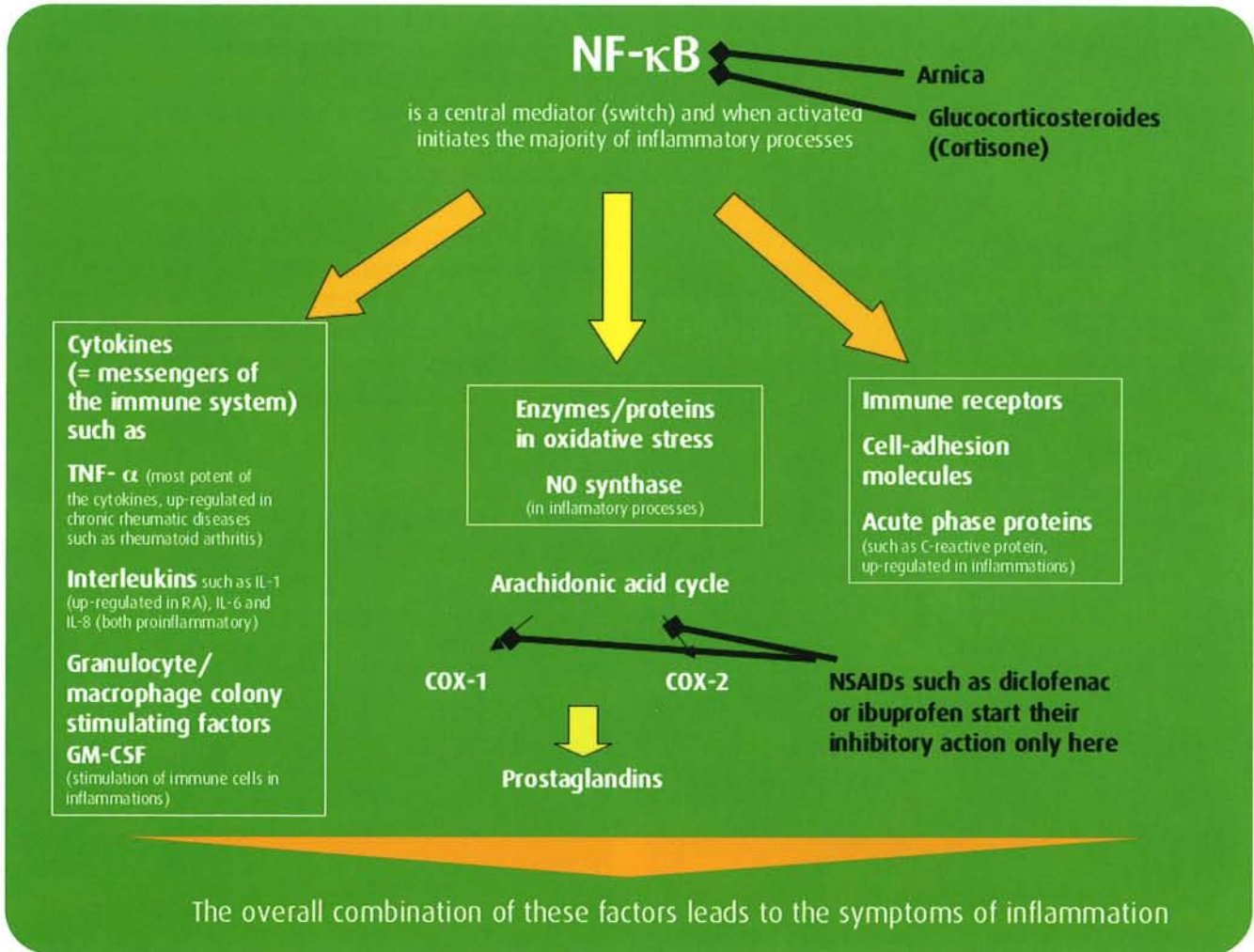


Figure 3: Diagram of the sites of action of arnica and NSAIDs in the inflammatory process

The described principle of action of the sesquiterpene lactones helenalin and 11 $\alpha$ ,13-dihydrohelenalin results in a beneficial effect on the inflammatory process. This is true particularly for chronic inflammations such as rheumatic complaints in which a raised level of the inflammatory mediators IL-1, IL-6 and TNF- $\alpha$  occurs.

**1.5.2 Antibiotic action**

The alkylation of particularly exposed sulphhydryl groups by the sesquiterpene lactones via a form of Michael addition is also responsible for the antibiotic action of arnica extract.<sup>17,18</sup> A structural chemical requirement for the antibacterial action is the  $\beta$ -unsubstituted cyclopentane ring, and to a lesser extent also an exomethylene group.<sup>18</sup> The spectrum of action covers Gram-positive and in rare cases also Gram-negative bacteria.<sup>17</sup>

In-vitro studies and preclinical studies document the analgesic and anti-inflammatory action of arnica. Today, arnica extract is used only in topical form, but there is still a wide range of indications.

## 2.1 Use

Arnica is available in the form of tinctures, ointments and gels exclusively for external use. The internal use of arnica common in middle ages is advised against for reasons of its toxicity. The toxic action is caused by the sesquiterpene lactones, which when administered internally can cause irritation to the gastric mucosae, nausea, vomiting and diarrhoea, and even collapse if large amounts are ingested.<sup>8</sup>

## 2.2 Efficacy

An assortment of studies (in vitro and in vivo) have investigated the efficacy of arnica preparations and the analgesic anti-inflammatory components. The individual subjects examined have been the inhibition of the transcription factor NF- $\kappa$ B by arnica gel<sup>19,20</sup> in vitro, the skin permeation of arnica preparations<sup>21</sup>, and the efficacy of arnica gel in joint and muscle complaints<sup>22,23</sup> and in chronic venous failure due to varicoses.<sup>24</sup>

### 2.2.1 Efficacy of arnica gel in vitro

The efficacy of arnica gel with regard to inhibition of the transcription factor NF- $\kappa$ B was investigated in vitro. It was shown that a gel prepared from fresh arnica flowers is a potent inhibitor of the transcription factor.<sup>19</sup> Another study showed the superiority of a gel prepared from fresh arnica flowers (A.Vogel Rheumatism Gel) even over other commercial preparations with regard to NF- $\kappa$ B inhibition. The transcription factor NF- $\kappa$ B is inhibited at a concentration of just 20  $\mu$ l/ml with the gel, whereas the other products had to be used at far higher concentrations.<sup>20</sup>

### 2.2.2 Permeation experiments with arnica preparations

Topically applied gels are particularly suitable for use in localised rheumatic complaints, because they can be applied easily and penetrate into the skin well. In a permeation study on a pig skin model, Wagner S. et al. determined the concentration of active substances reached in different layers of skin and also the depth to which the active substances penetrate. The study investigated the permeation behaviour of isolated individual sesquiterpene lactones, as well as the behaviour of tinctures and a gel. Arnica preparations were shown to penetrate as far as the stratum corneum, with the arnica gel being superior to the tincture or the isolated substance.<sup>21</sup> (Figure 4)

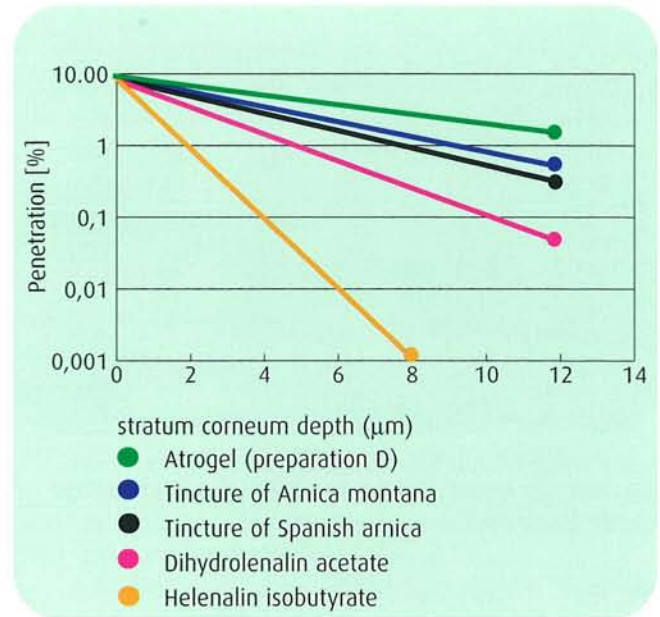


Figure 4: Comparison of the permeation of isolated sesquiterpene lactones, arnica tincture and arnica gel (A.Vogel Rheumatism Gel) in a skin model. The steeper the line, the worse the penetration of the test substance.<sup>21</sup>

### 2.2.3 Efficacy of arnica gel in clinical studies

#### Osteoarthritis

The open multicentre study by Knuesel et al. investigated the efficacy of an arnica gel in patients (n = 79) with mild to moderate osteoarthritis and/or peri-arthropathy of at least one knee joint by applying the gel to the affected site twice daily (morning and evening) for 6 weeks.<sup>22</sup> Efficacy was measured using the WOMAC Osteoarthritis Index, which is a validated parameter for assessing osteoarthrose. In addition, the study doctors and patients gave their own overall assessment of the efficacy at the end of the study. With the median of the WOMAC index in the ITT analysis falling from 36.0 points to 28.0 points, a highly significant improvement could be stated ( $p < 0.0001$ ). Significant treatment success was evident after just 3 weeks of treatment, and even more after 6 weeks (Figure 5).

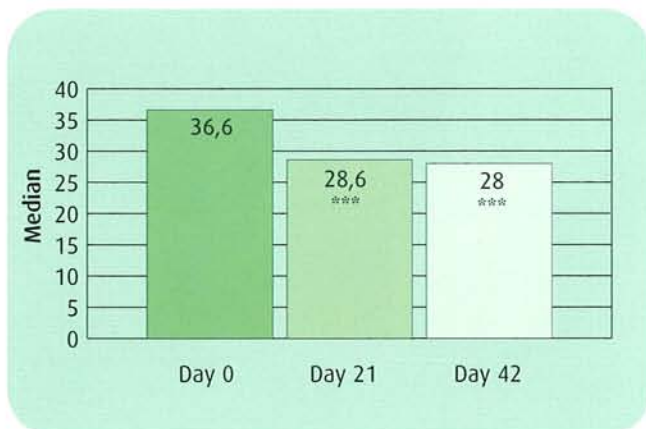


Figure 5: Reduction in the WOMAC median within the 6-week treatment ( $p < 0.0001$ , statistically highly significantly different relative to day 0)<sup>22</sup>

The study doctors reported an action in 76.7% of the treated patients and rated the efficacy as good to very good in 56.1% of cases. Arnica gel can be recommended as an effective and well tolerated medication for the treatment of mild and moderate forms of osteoarthritis of the knee.

### Muscle soreness

The action of an arnica gel in muscle soreness was investigated in comparison with placebo in a double-blind study ( $n = 12$ ). After a duration of use of 6 days, better symptom reduction occurred under arnica gel than under placebo, and no side effects or intolerability reactions were observed.<sup>23</sup>

### Venous complaints

The action of arnica gel in comparison with a combination ointment (of arnica flowers, chamomile oil and guaiazulene) in primary varicosis was investigated on 30 patients. The products were each rubbed in four times daily for three weeks. Both the monotherapy ( $p < 0.05$ ) and the combination therapy ( $p < 0.01$ ) showed a significant reduction in venous capacity and venous outflow rate, which can be assessed as a sign of vascular toning.<sup>24</sup>

Uehlecke B et al. also investigated the action of topical arnica preparations on chronic venous failure due to varicoses. After three weeks of treatment, the patients under arnica gel ( $n = 89$ ) and those under arnica ointment ( $n = 79$ ) showed a marked improvement in subjective symptoms relative to the starting situation and to placebo. Both active treatment groups showed a significant reduction in venous capacity in comparison with placebo.<sup>25</sup>

### 2.3 Perspectives on other options for use

Arnica is generally an effective symptomatic treatment option for all topically treatable complaints with an inflammatory component. These include not just sports injuries such as sprains, strains and bruises but also a large number of rheumatic diseases.

It is today known that the chronic inflammation in **rheumatoid arthritis** is triggered mainly by raised secretion of TNF- $\alpha$  and over-regulation of NF- $\kappa$ B. The inflammation can be combated effectively by inhibition of NF- $\kappa$ B. Individual case reports show that arnica gel is very effective particularly with the smaller joints that are most commonly affected.

In addition, first results from a clinical study with arnica gel in **finger polyarthritis** show that the gel is equally as effective as ibuprofen gel when administered for 3 weeks.<sup>26</sup>

The ESCOP monograph<sup>27</sup> also recommends arnica preparations in the buccal cavity in **gingivitis** and **aphthous ulcers**, and as a remedy for **insect stings**.

### 2.4 Tolerability

The external use of arnica can be rated as safe and well tolerated. Studies on arnica gel and ointments with durations of treatment of 6 days to 6 weeks recorded few intolerability reactions or adverse events.<sup>23,24,25</sup>

#### 2.4.1 Contact allergies due to *Arnica montana*

The literature frequently mentions *Arnica montana* in connection with contact allergies. The reasons for this may be firstly its high sensitisation potential<sup>28</sup> and secondly its relatively low toxic threshold.<sup>29</sup> The compounds responsible for the allergenic action of *Arnica montana* are once again the sesquiterpene lactones with an  $\alpha$ -methylene group on the  $\gamma$ -lactone ring<sup>30</sup>, and thus helenalin and its ester derivatives.<sup>28</sup>

Contact allergies occur comparatively rarely when arnica preparations are used properly.<sup>31</sup> For example, Knuesel et al.<sup>22</sup> investigated the efficacy of arnica gel in osteoarthritis and found allergic contact dermatitis in only 1 of 79 patients. Other studies support this finding. In epidermal testing with a composite mix, only 1.4% of healthy test subjects reacted to arnica extract.<sup>32</sup> In another allergy study, only 1% of 202 investigated patients with an allergy demonstrated a positive finding on contact with arnica tincture.<sup>33</sup>

A.Vogel Rheumatism Gel, the arnica gel of Bioforce AG, conforms with the most stringent qualitative requirements set for a modern medicinal product. The fresh arnica flowers originate from controlled biological cultivation in Germany and are then processed non-aggressively. The plants contain a large number of substances which exert their curative action only in combination. The amount and concentration of the individual constituents depend on the selected arnica species, the location, the harvesting time/harvesting conditions, the weather, and the cultivation conditions.

In order to ensure uniform concentrations of all constituents, Bioforce products are standardised by using 3 measures:

- The controlled biological cultivation always at the same site with the same seed guarantees a uniform plant quality.
- The validation of all critical manufacturing steps allows exact monitoring and regulation of production.
- The mixture of different batches to form annual mixes results in uniform active substance concentrations.

All the measures ensure consistently high product quality with optimum efficacy.

### 3.1 Specialist data sheet

#### A.Vogel Rheumatism Gel

For adjunct external use in rheumatism, arthritis, osteoarthritis and gout as well as in pain and inflammations of the joints and muscles such as muscle strains, muscle soreness, neck stiffness, back pain and lumbago.

#### Composition

1 g of A.Vogel Rheumatism Gel contains 500 mg of extract from fresh arnica flowers\* (Arnicae floris recentis tinctura 500 mg; drug/extract ration 1:20). This product contains additional excipients.

\*from controlled biological cultivation

#### Properties/actions

A.Vogel Rheumatism Gel possesses anti-inflammatory, antiseptic, antiphlogistic and blood-flow promoting properties. The anti-inflammatory action is based mainly on inhibition of the central inflammation mediator NF- $\kappa$ B, which results in the blocking of pro-inflammatory processes at their initial stages. In inflammations of joints and soft tissues, A.Vogel Rheumatism Gel has been proven to relieve pain and accelerate recovery of functionality.

#### Pharmacokinetics

Penetration measurements using a validated skin model showed that skin penetration by A.Vogel Rheumatism Gel is better than that by pure active principal substances or by the tincture. On average, about 10% of the constituents penetrate to the lowest layers of the stratum corneum.

More detailed information on the distribution, metabolism and elimination is not available.

#### Indication/options for use

As an adjunct measure in rheumatism, arthritis, osteoarthritis and gout, the gel is indicated for external use in pain and inflammations of the joints and muscles such as muscle strains, muscle soreness, neck stiffness, back pain and lumbago.

#### Dosage/application

Unless otherwise prescribed, a 4 cm strand of A.Vogel Rheumatism Gel is applied to the affected area twice daily and rubbed in gently.

#### Restrictions on use

Hypersensitivity (allergy) to arnica and Asteraceae (sunflowers) and to the other constituents of the product.

#### Adverse actions

In exceptional cases, arnica preparations can cause allergic skin reactions.

#### Interactions

No available data

#### Other notes

##### Shelf-life

The medicament may be used only up to the date marked EXP on the container.

#### Swissmedic number

56199

#### Packs

In tubes of 100 ml (95 g). List D. Covered by health insurance at a basic level.

#### Version of data sheet

November 2002

Arnica montana has since the middle ages had an established place as a cure-all remedy in folk medicine. On the basis of recently performed in-vitro and in-vivo studies, the topical use of arnica extract can also be seen to be scientifically based.

Clinical investigations demonstrate that, in particular, the sesquiterpene lactones helenalin and 11 $\alpha$ ,13-dihydrohelenalin contained in arnica inhibit the transcription factor NF- $\kappa$ B, a central mediator in inflammatory reactions. The use of arnica thus exerts a pain-relieving and inflammation-inhibiting action in the early stages of the process.

A.Vogel Rheumatism Gel, the gel from fresh arnica flowers, is an effective adjuvant and low side effect therapy in traumatic, inflammatory and degenerative complaints of joints and soft tissues.

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